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CLINICAL RESEARCH

Interventional Cardiology

Sex Differences in Mortality After Transcatheter Aortic Valve Replacement for Severe Aortic Stenosis

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Objectives The aim of this study was to examine sex differences in outcome after transcatheter aortic valve replacement (TAVR) with real-world data from 2 large centers in Canada.

Background Transcatheter aortic valve replacement is an effective alternative to surgical valve replacement in symptomatic patients with severe aortic stenosis, but the impact of sex on outcomes remains unclear. The PARTNER (Placement of Aortic Transcatheter Valves) 1A trial demonstrated greater benefit of TAVR over surgery in women, but whether this was due to the poorer surgical outcome of women or better TAVR outcome, compared with men, is unknown.

Methods Consecutive patients (n = 641) undergoing TAVR in Vancouver and Quebec City, Canada, were evaluated. Differences in all-cause mortality were examined with Kaplan-Meier estimates, adjusted logistic regression, and proportional hazards models.

Results Women comprised 51.3% of the cohort. Balloon-expandable valves were used in 97% of cases, with transapical approach in 51.7 % women and 38.1% men. Women had more major vascular complications (12.4% vs. 5.4%, p = 0.003) and borderline significantly more major/life-threatening bleeds (21.6% vs. 15.8%, p = 0.08). At baseline, women had higher aortic gradients and worse renal function but better ejection fractions. Men had more comorbidities: prior myocardial infarction, prior revascularization, and chronic obstructive pulmonary disease. The adjusted odds ratio for 30-day all-cause mortality favored women, 0.39 (95% confidence interval: 0.19 to 0.80; p = 0.01), and this benefit persisted for 2 years, hazard ratio 0.60 (95% confidence interval: 0.41 to 0.88; p = 0.008).

Conclusions Female sex is associated with better short- and long-term survival after TAVR. Added to the PARTNER 1A findings, these results suggest TAVR might be the preferred treatment option for elderly women with symptomatic severe aortic stenosis. (J Am Coll Cardiol 2012;60:882–6) © 2012 by the American College of Cardiology Foundation

Untreated patients with symptomatic aortic stenosis (AS) experience a high rate of death (1,2). Surgical aortic valve replacement improves both symptoms and survival; but with advanced age, poor left ventricular function, or comorbid conditions, operative mortality and complications can be high (3,4). In such patients, transcatheter aortic valve replacement (TAVR) is an effective alternative (5,6). However, the effect of sex on outcomes after TAVR remains unclear. In the randomized PARTNER (Placement of Aortic Transcatheter Valves) 1A trial, a pre-specified subgroup analysis suggested the mortality benefit of TAVR over surgical replacement at 1 year was greater in women (6). Further examination of the data from the TAVR-only arm demonstrates greater benefit in women but without adjustment for potential baseline differences between women and men. Further investigation of this potential benefit is warranted.

Three recent publications examined sex differences in outcomes after TAVR. A single-center study of 305 high-

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risk patients undergoing TAVR found no sex difference in 30-day mortality but a higher rate of vascular complications and bleeding in women (7). Another study of 260 consecutive TAVR patients reported better 1-year survival in women (8) but failed to adjust for baseline characteristics, which varied substantially between men and women. A brief report on sex differences in 333 consecutive patients with a Medtronic CoreValve (Medtronic, Inc., Irvine, California) found no sex differences in 30-day or 1-year mortality (9).

With limited and conflicting evidence of sex differences in TAVR outcomes, we evaluated patients who underwent TAVR in 2 high-volume centers in Canada.

Methods

Study cohort. Consecutive, high-risk patients with severe AS undergoing TAVR between January 2005 and September 2011 at St. Paul's Hospital (Vancouver, Canada; n = 468) and the Quebec Heart and Lung Institute (Quebec City, Canada; n = 199) were prospectively captured in a database. All symptomatic patients with severe AS, at high or prohibitive risk for conventional surgery, were selected for TAVR after review by a dedicated heart team comprising interventional cardiologists and cardiac surgeons. Exclusions included unsuccessful TAVR (i.e., the valve could not be implanted) (n = 7) or transcatheter heart valve implantation in an existing bioprosthetic valve (n = 19). The final cohort comprised 641 patients with successful placement of a transcatheter heart valve in a native valve. All patients provided written informed consent. Postoperative assessment occurred at 1, 6, and 12 months and annually thereafter.

TAVR procedure. The TAVR was performed with balloon-expandable valves, Cribier-Edwards, Edwards SAPIEN, Edwards SAPIEN XT (Edwards Lifesciences, Inc., Irvine, California) and self-expanding valves (CoreValve, Medtronic Inc.; Portico, St. Jude Medical, St. Paul, Minnesota; CENTERA, Edwards Lifesciences). Four valve sizes were used: 20, 23, 26, and 29 mm. Transfemoral access was the preferred route, except in patients with unsuitable iliofemoral arteries.

Endpoints. The primary endpoints were 30-day all-cause mortality and 2-year survival. Safety endpoints—vascular complications, bleeds, stroke—were defined according to the Valve Academic Research Consortium criteria (10).

Statistical analysis. Results are expressed as counts and percentages for categorical variables and medians and 1st and 3rd quartiles for continuous variables, due to skewed distributions. Differences in baseline characteristics were tested with the Mann-Whitney *U* test for continuous variables and the chi-square test for categorical variables.

Sex difference in survival was first evaluated with Kaplan-Meier curves. Multiple logistic regression analysis was used to examine the independent sex effect on 30-day mortality. All clinically important variables were included in the model. In addition, variables unbalanced between men and women or with univariate analysis p values <0.25 for association with mortality were evaluated; and only those that improved the model fit, on the basis of the Akaike Information Criterion for model selection, were kept in the final fully adjusted model. A parsimonious model was also built from the fully adjusted model with the backward elimination method with p = 0.10.

The association between sex and 2-year survival was examined with the Cox proportional hazards model. The proportional hazard assumption was assessed by a Kolmogorov-type supremum test. Multivariable Cox models were built in

Abbreviations and Acronyms

AS = aortic stenosis

AVA = aortic valve area

CI = confidence interval

EF = ejection fraction

HR = hazard ratio

TAVR = transcatheter aortic valve replacement

Table 1 Baseline Characteristics

Characteristic	Female (n = 329)	Male (n = 312)	p Value
Age, yrs	83 (76, 87)	82 (76, 86)	0.55
STS-PROM score	7.5 (5, 10.2)	7.5 (4.8, 10.9)	0.76
AVA, cm^2	0.6 (0.5, 0.7)	0.7 (0.6, 0.8)	<0.001
AVA index, cm^2/m^2	0.35 (0.30, 0.43)	0.35 (0.30, 0.41)	0.36
Mean aortic gradient	41 (32, 53)	40 (30, 51)	0.01
Body surface area, m^2	1.6 (1.5, 1.8)	1.9 (1.8, 2.0)	<0.001
MR grade III/IV	99 (30.3)	67 (21.6)	0.01
AR grade III/IV	20 (6.2)	18 (5.8)	0.84
NYHA III/IV	287 (87.2)	267 (85.6)	0.54
EF	60 (55, 65)	55 (40, 60)	<0.001
EF			<0.001
<30%	12 (3.6)	28 (9.1)	
30% to <60%	87 (26.4)	140 (45.3)	
60%+	230 (69.9)	141 (45.6)	
CAD	211 (64.1)	256 (82.6)	<0.001
Prior MI	117 (35.8)	142 (45.5)	0.01
Prior revascularization	130 (39.5)	198 (63.5)	<0.001
Atrial fibrillation	107 (32.5)	121 (38.9)	0.09
Heart failure	232 (70.7)	232 (74.4)	0.30
COPD	70 (21.3)	100 (32.1)	0.002
Cerebrovascular disease	52 (15.9)	66 (21.4)	0.07
Hypertension	264 (80.2)	242 (77.6)	0.41
Peripheral vascular disease	96 (29.3)	108 (35.8)	0.13
Diabetes	99 (30.1)	98 (31.4)	0.72
eGFR, ml/min	48 (36, 64)	53 (38, 69)	0.05
eGFR, ≥60 ml/min	103 (31.8)	125 (40.2)	0.03
Hemodialysis	5 (1.5)	11 (3.5)	0.10
Frailty	135 (41.3)	98 (31.6)	0.01
Porcelain aorta	92 (29.2)	37 (12.0)	<0.001
Smoking			<0.001
None	240 (72.9)	142 (45.5)	
Remote	80 (24.3)	147 (47.1)	
Current	9 (2.7)	23 (7.4)	

Values are median (Q1, Q3) or n (%).

AR = aortic regurgitation; AVA = aortic valve area; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; MR = mitral regurgitation; NYHA = New York Heart Association functional class; STS-PROM score = Society of Thoracic Surgeons Predicted Risk of Mortality score.

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Table 2 Functional Characteristics After Transcatheter Heart Valve Implantation

Characteristic	n*	Female	Male	p Value
AVA	502	1.40 (1.20, 1.60)	1.62 (1.40, 1.90)	<0.001
AVA index, cm^2/m^2	502	0.85 (0.73, 1.00)	0.86 (0.74, 1.01)	0.43
Change in AVA index	500	0.49 (0.36, 0.63)	0.52 (0.39, 0.67)	0.21
Mean aortic gradient	591	11 (8, 14)	10 (7, 12)	0.003
Change in mean aortic gradient	582	−31 (−43, −22)	−29 (−41.5, −20)	0.10
MR grade III/IV	616	45 (14.2)	41 (13.7)	0.86
AR grade III/IV	597	5 (1.6)	9 (3.1)	0.24
EF	612			<0.001
<30%		11 (3.5)	22 (7.4)	
30% to <60%		79 (25.1)	119 (40.1)	
≥60%		225 (71.4)	156 (52.5)	

Values are median (Q1, Q3) or n (%). *Cases with non-missing values.
Abbreviations as in Table 1.

stages to examine the influence of demographic, procedural, and clinical factors as well as procedural complications on the sex difference in survival.

A 2-sided p value of <0.05 was considered statistically significant. Statistical analyses were performed with SAS software (version 9.2, SAS, Cary, North Carolina).

Results

Women comprised 51.3% (n = 329) of the final cohort. There were no significant sex differences in age, Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score, aortic valve area (AVA) index, aortic regurgitation grade, and New York Heart Association functional class. Women had higher mean aortic gradients, worse renal function, and more porcelain aortas than men but better ventricular function. Although women were more often frail, the prevalence of most comorbid conditions was higher in men, including coronary artery disease, prior myocardial infarction, prior revascularization, and chronic obstructive pulmonary disease (Table 1).

The balloon-expandable valves, Cribier-Edwards (9%), Edwards SAPIEN (56%), and SAPIEN XT (32%) were most commonly used. Larger valves (26 and 29 mm) were deployed in more men (88.8%) than women (29.5%) ($p < 0.001$). More women (52%) than men (38%) had a transapical approach ($p < 0.001$).

Improvements in AVA index and mean aortic gradient after the procedure did not differ between the sexes. Mean aortic gradient and left ventricular ejection fraction remained higher in women (Table 2).

The 30-day rates of stroke and permanent pacemaker implantation did not differ by sex (Table 3). Women had more major/life-threatening bleeds (21.6% vs. 15.8%), more blood transfusion (9.5% vs. 3.6%), and more major vascular complications (12.4% vs. 5.4%).

More men (11.2%) than women (6.5%) died by 30 days (p = 0.05). After adjusting for aortic regurgitation grade III/IV, mitral regurgitation grade III/IV, access route, estimated glomerular filtration rate, heart failure, chronic obstructive pulmonary disease, prior myocardial infarction, coronary artery disease, STS-PROM score, AVA index, mean aortic gradient, prior revascularization, porcelain aorta, ejection fraction, and site, the female odds ratio for 30-day mortality was 0.39 (95% confidence interval [CI]: 0.19 to 0.80). In a parsimonious model, with only the first 5 covariates, the female odds ratio was 0.37 (95% CI: 0.19 to 0.72).

Median follow-up was 302 days (interquartile range: 44 to 712 days). The Kaplan-Meier survival curves demonstrate a significant survival advantage for women, log-rank test p = 0.007 (Fig. 1). The 1- and 2-year survival estimates were 82.7% (95% CI: 77.4% to 86.8%) and 72.1% (95% CI: 65.0% to 78.0%), respectively, for women and 72.5% (95% CI: 66.4% to 77.7%) and 61.7% (95% CI: 54.1% to 68.3%), respectively, for men.

In the Cox model for all-cause mortality up to 2 years, the unadjusted hazard ratio (HR) for female sex was 0.64 (95% CI: 0.46 to 0.88). The Cox model was then adjusted, incrementally, for grouped baseline characteristics (Table 4). After adjustment for age, site, and access route, the female HR was 0.58 (95% CI: 0.41 to 0.82). After adding baseline aortic valve characteristics (AVA index, mean gradient, grade of regurgitation), STS-PROM score, and grade of mitral regurgitation, the HR was 0.59 (95% CI: 0.42 to 0.84). Further adjustment for baseline comorbid conditions gave an HR of 0.60 (95% CI: 0.41 to 0.88). After adding

Table 3 30-Day Post-Procedural Complications and Outcomes

Event	Total (n = 584)*	Female (n = 306)	Male (n = 278)	p Value
Major vascular complication	53 (8.6)	38 (12.4)	15 (5.4)	0.003
Major/life-threatening bleed	110 (17.3)	66 (21.6)	44 (15.8)	0.08
Blood transfusion	39 (6.7)	29 (9.5)	10 (3.6)	0.005
Major stroke	11 (1.9)	6 (2.0)	5 (1.8)	0.89
New pacemaker	32 (5.5)	20 (6.4)	12 (4.3)	0.24
30-day mortality	51 (8.7)	20 (6.5)	31 (11.2)	0.05

Values are n (%). *Excluded 57 cases without 30 days of follow-up.

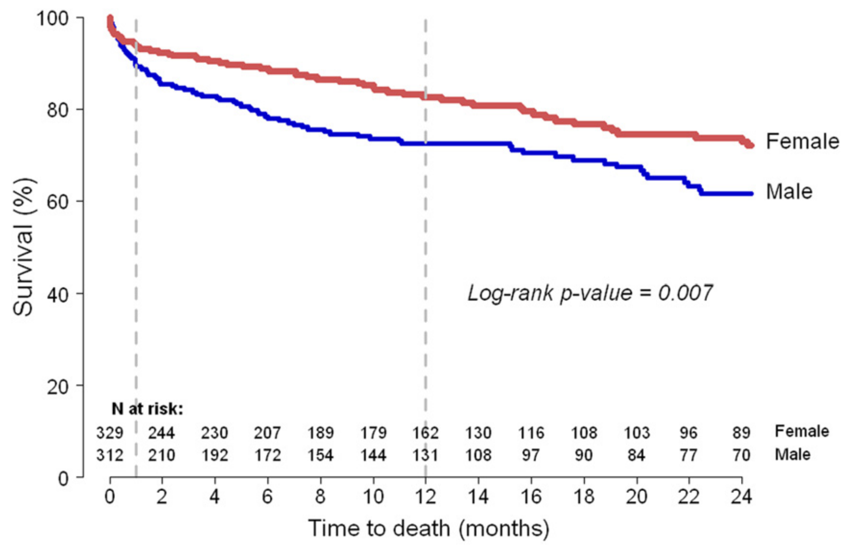

Figure 1 **Kaplan-Meier Plot for All-Cause Mortality**

Women's survival advantage at 30 days and throughout the 2-year follow-up period.

post-procedural complications (i.e., vascular and major/life-threatening bleeding), the female HR was 0.55 (95% CI: 0.37 to 0.81; p = 0.003).

Discussion

In a large cohort of elderly subjects undergoing TAVR for severe AS, female sex was associated with significantly better survival, both at 30 days and up to 2 years, even after adjustment for demographic, procedural, and clinical factors.

In a finding consistent with other studies, women had more vascular complications and major/life-threatening bleeds. Yet despite these adverse events, all-cause mortality remained lower in women.

The PARTNER 1A subgroup analysis demonstrated a greater survival benefit with TAVR compared with surgery in women (risk ratio: 0.68; 95% CI: 0.44 to 1.04) than men (risk ratio: 1.17; 95% CI: 0.84 to 1.63), $p_{interaction}$ = 0.05.

Table 4 **Influence of Incremental Adjustment on Cox Models of Female HR for Mortality**

Model	HR*	95% CI	p Value
Sex (unadjusted)	0.64	0.46–0.88	0.007
Model 1 + age, access route, site	0.58	0.41–0.82	0.002
Model 2 + STS-PROM, AVA index, MR, AR, mean gradient	0.59	0.42–0.84	0.003
Model 3 + eGFR, EF, AF, COPD, prior MI, CAD, frailty	0.60	0.41–0.88	0.008
Model 4 + major vascular complications, major/life-threatening bleeding complications	0.55	0.37–0.81	0.003

*Female versus male sex.
AF = atrial fibrillation; CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

Within the TAVR arm, mortality was lower in women (18.4%) than men (28.4%) (p = 0.03); after surgical valve replacement the rates for men (24.2%) and women (27.2%) were similar (p = 0.54). Because there might be imbalances in baseline characteristics between the sexes, the demonstrated female advantage in the TAVR arm should be considered suggestive rather than definitive.

Hayashida et al. (8) also reported better female survival after TAVR, but no adjustment was undertaken for sex differences in baseline characteristics. In contrast to our findings and others (7), Hayashida et al. (8) did not find more major vascular events in women. Major/life-threatening bleeds were not reported. Of note, crude all-cause mortality rates at 30 days were much higher than in our study: 17.8% versus 11.2% in men; 12.2% versus 6.5% in women.

It is unlikely the observed female advantage can be explained by the observed baseline differences, given that extensive adjustment for demographic, procedural, and clinical differences failed to attenuate the sex difference. Sex has been shown to impact cardiac remodeling and fibrosis (11,12). Specifically, cardiac hypertrophy in patients with severe AS develops differently in women than men. Interstitial fibrosis is more pronounced in male hearts, as is collagen I, II, and matrix metalloproteinase expression. Lower levels of fibrosis in women might underpin the more rapid reversal of myocardial hypertrophy after correction of AS and might partially explain the better outcome in women compared with men (13).

Strengths and limitations. Comprehensive data collection and follow-up of TAVR patients at St. Paul's Hospital and the Quebec Heart and Lung Institute provided a rich clinical dataset that allowed us to adjust our models for clinical, demographic, and procedural factors. However, we cannot exclude the possibility of unmeasured confounders. The study is limited to 2 large centers that predominately used balloon-expandable devices. The results might not be generalizable to other centers and other types of valves.

Conclusions

This is the largest study to date of sex differences in outcomes after TAVR in the "real world." Women had significantly better survival, both short- and longer-term, despite higher rates of major/life-threatening bleeding and vascular complications. The results, when considered in the context of the PARTNER 1A findings, suggest TAVR might be the preferred mode of treatment in elderly women with symptomatic severe AS.

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